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Use of All-Trans Retinoic Acid to Treat Acute Promyelocytic Leukemia: A Case With Very Severe Features at the Onset in Nicaragua

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We observed a child with acute promyelocytic leukemia (APL) who, at the onset, had extremely severe hemorrhagic and septic complications. According to our experience in Nicaragua, there was a very high risk of early death. The patient was successfully treated with all-trans retinoic acid (ATRA) followed by cytotoxic chemotherapy. ATRA has two important features: it is effective in initial treatment of APL and it is inexpensive. Because of the high cost and the need for extensive supportive care, optimal myeloablative therapy used in patients with various types of acute myeloid leukemia generally cannot be given in developing countries. ATRA treatment for APL is affordable everywhere.

Key words: acute promyelocytic leukemia, all-trans-retinoic acid, childhood, developing countries

INTRODUCTION

Acute promyelocytic leukemia (APL) has unique clinical and biological features [1,2] and is associated with a relatively high rate of early mortality primarily from hemorrhage and infectious complications. However, after achieving remission, these patients have a greater probability of prolonged disease-free survival than those affected by other subtypes of acute myeloid leukemia (AML). APL seems to occur with a higher frequency in children than was generally thought in the past. Geographical clusters also have been seen in some developing countries [3]. The treatment of APL and other AML subtypes is usually considered to be nonaffordable in developing countries because of the inadequacy of laboratory and clinical facilities and the shortage of the drugs and blood products needed for supportive care.

We report here the case of a child in Nicaragua with APL who had extremely severe complications at the onset, with multiple necrotic and suppurative skin lesions, severe generalized bleeding, and sepsis due to *Pseudomonas aeruginosa*. In spite of the extremely poor initial prognosis, the child was successfully treated with all-trans retinoic acid (ATRA).

CASE REPORT

A 10-year-old girl was referred, in October 1993, to La Mascota Hospital in Managua because of fever of 2 weeks duration, frequent hematemesis, and melena. On admission the hemoglobin (Hb) level was 9.3 g/dL, white blood count (WBC) was 14×10^9/L (87% blasts, 6% neutrophils, 7% lymphocytes), platelets (PLT) were 16×10^9/L. Prothrombin activity was 80%, partial thromboplastin time was 28 seconds, and fibrinogen was 308 mg/dL. The child was febrile (39°C) and presented with hematemesis, melena, and diffuse cutaneous bleeding. Multiple necrotic and suppurative skin lesions were observed. After curettage of the skin lesions, an intravenous infusion of ceftazidime and amikacin was started. Blood culture later grew *Pseudomonas aeruginosa*. Cultures from cutaneous lesions revealed the presence of *Klebsiella pneumoniae* and *Staphylococcus aureus*.

A diagnosis of APL was established according to FAB criteria using May-Grünwald Giemsa staining of peripheral blood and bone marrow smears [4]. The myeloperoxidase stain was intensely positive. No cytogenetic studies were done. Molecular analysis was performed in Italy on DNA recovered from frozen bone marrow cells and revealed the presence of RAR-alpha and PML gene rearrangements [5].

Initial treatment consisted of ATRA given as a single agent at the dose of 45 mg/m^2 daily. Heparin was admin-

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istered from days 1–15 at 100 IU/Kg/day i.v. by continuous intravenous infusion. Packed red blood cells and platelet concentrates were also transfused when necessary, until day 15. On day 5, the leukocyte count was 46×10^9/L (blasts 52%, neutrophils 43%, lymphocytes 4%, monocytes 1%). Therefore, cytosine arabinoside 100 mg/m^2/day was administered on days 5–8 in addition to ATRA. On day 8, the WBC was 8.0×10^9/L (blasts 19%, neutrophils 58%, lymphocytes 8%, myelocytes 12%, metamyeloytes 3%).

During this phase of treatment, no significant abnormalities of coagulation tests were observed. Absolute neutrophil counts, never below 0.5×10^9/L, progressively increased. After day 17, platelets were >30.x 10^9/L. On day 18, the patient became afebrile. No toxicity related to ATRA was observed.

On day 36, the child was in good clinical condition. Repeated bone marrow aspirate showed complete remission (CR) by morphological criteria. The Hb level was 11.6 g/dL, WBC was 4.9×10^9/L (neutrophils 68%, lymphocytes 27%, monocytes 3%, eosinophils 2%), PLT count 200×10^9/L. ATRA was discontinued. Subsequent treatment was given according to AML-BFM-83 consolidation and maintenance schedules [6]. Seven months after the onset, the child remains in CR and in good condition.

DISCUSSION

Results obtained with conventional chemotherapy in APL differ considerably from those obtained in other subtypes of AML. Conventional induction treatment is frequently associated with early death from coagulation disorders during the first days of treatment, or due to sepsis during the phase of marrow aplasia [1,2,7,8]. However, over the last few years, ATRA has been shown to produce a higher rate of CR than standard chemotherapy by reducing the incidence of early death [2,9].

The hemorrhagic disorder associated with APL is due to a complex interaction of several processes. The bleeding diathesis is triggered by the lysis of APL blasts and by the release of procoagulant activites, plasminogen activators, and proteases [10]. During standard cytotoxic treatment of these patients, heparin has been recommended, although there is no definitive proof of its benefit [10,11]. By contrast, differentiation therapy with ATRA resolves the coagulopathy (as assessed by standard coagulation tests) within the first few days of treatment, even before any morphologic effects on APL cells become apparent [12]. The use of heparin in patients receiving ATRA alone, when there is no marked or persistent elevation of fibrin-degradation products (as evidence of DIC), might be questionable. Recently it was reported that ATRA may more rapidly reverse proteolysis than decrease procoagulant activity [13]. This imbalance between proteolytic and procoagulant activities may be partially responsible of the thrombotic events observed in patients who develop hyperleukocytosis during the course with ATRA treatment [13].

Patients treated with ATRA achieve CR in 1–3 months without undergoing bone marrow aplasia. It is of interest to note that morphologically atypical neutrophils induced by ATRA, which appear in the peripheral blood, are functionally similar to normal neutrophils except for decreased chemotaxis [14]. These neutrophils may be useful in combating infections.

Treatment of APL is very difficult with conventional chemotherapy in developing countries. At La Mascota Hospital in Managua, we observed a very high incidence of early hemorrhagic and septic deaths during conventional cytotoxic treatment of APL in children [15]. The case described in this report was extremely severe and, according to our experience, was at high risk for early death. Treatment with ATRA prevented neutropenia and blood coagulation disorders, allowed successful therapy of the life-threatening infections by conventional antibiotics, and led to a rapid achievement of CR.

Treatment with ATRA is easier and cheaper than conventional cytotoxic treatment. Toxicity has been reported to be frequent in children treated with this drug at doses of 45 mg/m^2 per day [16]. No difference in therapeutic efficacy has been observed when ATRA was given at 25 mg/m^2 per day [17]. Further studies are needed to define the most effective and least toxic dose of this drug.

In conclusion, our experience strongly supports the use of ATRA in the treatment of patients with APL even in developing countries.

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